CLINICAL REVIEW

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Recommend approving NDA 21-690 and incorporating the following sentence (revised wording is underlined) into the Ortho Tri-Cyclen Prescribing Information, **PRECAUTIONS** section, **Pediatric Use** subsection,

> Safety and efficacy of ORTHO TRI-CYCLEN Tablets and ORTHO CYCLEN Tablets have been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 16 and for users 16 years and older. There was no significant difference between ORTHO TRI-CYCLEN Tablets and placebo in mean change in total lumbar spine (L1-L4) and total hip bone mineral density between baseline and Cycle 13 in 123 adolescent females with anorexia nervosa in a double-blind, placebo-controlled, multicenter, one-year treatment duration clinical trial for the Intent To Treat (ITT) population. Use of this product before menarche is not indicated.

It should be noted that in the Complete Class 2 Response to Approvable Action Letter, letter date November 18, 2004, the sponsor had requested approval of the new indication "ORTHO TRI-CYCLEN is indicated for treatment to increase lumbar spine bone mineral density in adolescent females with anorexia nervosa." This new indication was not granted due to lack of efficacy in the CAPSS-169 ITT population at Cycle 13. On May 3, 2005, the sponsor accepted the Division proposed labeling and agreed to incorporate the above single new sentence into the Ortho Tri-Cyclen Prescribing Information, **PRECAUTIONS** section, **Pediatric Use** subsection.

1.2 Recommendation on Postmarketing Actions

This reviewer has no recommendations for any postmarketing actions.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The sponsor conducted one clinical study.

CAPSS-169 was a Phase 2, double-blind, randomized, placebo-controlled, multicenter, one-year treatment duration clinical study that evaluated the effect of Ortho Tri-Cyclen compared to placebo on bone mineral density in 123 adolescent females with anorexia nervosa. It seems likely that most, if not all, subjects, subject families, and investigators were unblinded due to the well-known changes in menses and adverse events associated with oral contraceptives.

1.3.2 Efficacy

At screening, the majority of the 123 subjects treated in CAPSS-169 did not meet either the DSM-IV diagnostic criteria for anorexia nervosa or the sponsor-modified DSM-IV diagnostic criteria for anorexia nervosa. Mean change in body weight from baseline to Cycle 13 was 6.73 kg for Ortho Tri-Cyclen subjects and 4.85 kg for placebo subjects.

In the ITT population (n=112), treatment with Ortho Tri-Cyclen from baseline to Cycle 13 (LOCF) was not associated with a significant change in mean total lumbar spine (L1-L4) bone mineral density when compared to placebo (0.0264 gm/cm^2 vs. 0.0190 gm/cm^2 p=0.244; 3.1% vs. 2.4% p=0.268). In the ITT population, treatment with Ortho Tri-Cyclen was not associated with a significant change in mean total hip bone mineral density from baseline to Cycle 13 when compared to placebo (0.0111 gm/cm^2 vs. 0.0133 gm/cm^2 p=0.784; 1.5% vs. 1.8 % p=0.724). In the ITT population in subjects with negative Z-scores at baseline, treatment with Ortho Tri-Cyclen was not associated with a significant change in mean total lumbar spine (L1-L4) BMD from baseline to Cycle 13 when compared to placebo (0.0286 gm/cm^2 vs, 0.0225 gm/cm^2 p=0.435). In the ITT population (n=112), treatment with Ortho Tri-Cyclen from baseline to Cycle 6 showed a statistically significant increase in mean total lumbar spine bone mineral density when compared with placebo (0.0197 gm/cm^2 vs. 0.0084 gm/cm^2 p=0.021; 2.4% vs. 1.0% p=0.013). However, the observed treatment difference (i.e., 0.011 gm/cm^2) between the two study groups was marginal and smaller than the expected difference (i.e., the basis for the power calculations for the trial) from baseline to Cycle 6 (0.05 gm/cm^2 or 6%). In addition, treatment with Ortho Tri-Cyclen was not associated with a significant change in mean total hip bone mineral density from baseline to Cycle 6 when compared to placebo (0.0100 g/cm^2 vs. 0.0019 gm/cm^2 p=0.146; 1.4% vs. 0.4% p=0.138). In sum, a clinically meaningful difference between Ortho Tri-Cyclen and placebo was not observed at Cycle 6 and neither a statistically or a clinically meaningful difference was observed at Cycle 13.

Multiple post-hoc analyses were performed by the sponsor and by the CDER statistician to evaluate subjects felt to have reasonably satisfied the criteria for anorexia nervosa at baseline and/or have not gained excessive weight during the trial. Per the sponsor, when subjects with a baseline BMI >18.5 kg/m^2 and/or IBW at Visit 1 >85% were excluded from the analysis, treatment with Ortho Tri-Cyclen was not associated with a significant change in mean total lumbar spine (L1-L4) BMD from baseline to Cycle 6 or to Cycle 13 when compared to placebo. Per the sponsor, when subjects with a weight gain of over 20 pounds from Visit 1 to last visit were excluded from the analysis, treatment with Ortho Tri-Cyclen was not associated with a significant change in mean total lumbar spine (L1-L4) BMD from baseline to Cycle 6 or to Cycle 13 when compared to placebo. Table 1 provides additional subgroup analyses performed by the NDA 21-690 CDER Statistical reviewer.

Table 1: CAPSS-169: Change from Baseline in Lumbar Spine BMD (gm/cm^2) at Cycle 13 for Special Defined Subgroups Performed by NDA 21-690 CDER Statistical Reviewer

ITT Population	Lumbar Spine BMD Raw Mean ± SD (N)		Treatment Difference	p-value
	Ortho Tri-Cyclen	Placebo		
BMI ≥ 10th percentile	0.0289 ± 0.0454 (35)	0.0201 ± 0.0329 (35)	0.0083	0.3887
BMI < 10th percentile	0.0214 ± 0.0476 (18)	0.0173 ± 0.0440 (24)	0.0108	0.3934

ITT Population	Lumbar Spine BMD Raw Mean ± SD (N)		Treatment Difference	p-value
	Ortho Tri-Cyclen	Placebo		
Subjects selected by MO for exclusion[1]	0.0299 ± 0.0236 (14)	0.0202 ± 0.0393 (12)	0.0108	0.4947
Subjects not selected by MO for exclusion	0.0251 ± 0.0518 (39)	0.0187 ± 0.0374 (47)	0.0087	0.3157
Weight ≥ 90% of IBW	0.0369 ± 0.0195 (14)	0.0262 ± 0.0367 (13)	0.0123	0.4226
Weight < 90% of IBW	0.0226 ± 0.0519 (39)	0.0170 ± 0.0379 (46)	0.0082	0.3450
Weight Change > 20 lbs	0.0262 ± 0.0329 (13)	0.0193 ± 0.0449 (10)	0.0038	0.8210
Weight Change ≤ 20 lbs	0.0265 ± 0.0497 (40)	0.0189 ± 0.0363 (49)	0.0105	0.2221
Negative Z-score	0.0286 ± 0.0492 (42)	0.0225 ± 0.0360 (49)	0.0078	0.3564
Non-negative Z-score	0.0180 ± 0.0303 (11)	0.0016 ± 0.0418 (10)	0.0182	0.3024

1 Subjects with high % of Visit 1 IBW, high baseline BMI, positive baseline lumbar spine BMD Z-score, and/or large weight gain were selected by the reviewing medical officer (MO) for exclusion.
2 Treatment difference and p-value were obtained using model with baseline lumbar spine BMD, treatment, subgroup, and treatment-by-subgroup.

1.3.3 Safety

There were no deaths, no pregnancies, and no reports of venous thromboembolic events during the conduct of CAPSS-169. Significantly more treated subjects on Ortho Tri-Cyclen prematurely discontinued from the study (n=21, 34.4%) than placebo subjects (n=13, 21.0%). This trial enrolled some subjects with primary amenorrhea. It is concerning that one subject was started on oral contraceptives and her imperforate hymen was not diagnosed until after 11 months on treatment. A visual examination of the vulva and vaginal introitus should have diagnosed the imperforate hymen at screening.

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